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Sleep disturbances in long-term immigrants with chronic mountain sickness: A comparison with healthy immigrants at high altitude

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ABSTRACT

The aim of this study was to examine sleep disturbances in patients with chronic mountain sickness (CMS). The sleep of 14 patients with CMS and 11 healthy controls with or without sleep disorders (control N: without sleep disorders; control D: with sleep disorders) was studied by polysomnography. Hypopnea was the sleep disorder most commonly suffered by CMS patients and control D subjects. No major differences were observed in sleep structure between CMS and control groups, with the exception of shorter rapid eye movement latency in controls and increased deep non-rapid eye movement in the control N group. Periodic breathing was observed in only two study participants, one each in the CMS and control D groups. The level of saturated oxygen was significantly lower in the CMS group during sleep than the control groups ($P < 0.05$). CMS scores were positively correlated with the apnea–hypopnea index, and negatively correlated with saturated oxygen levels. These results demonstrate that sleep disorders and nocturnal hypoxia are important in the development of CMS.

1. Introduction

Chronic mountain sickness (CMS) is a clinical syndrome that occurs at elevations above 2500 m and affects both natives and immigrants who reside at high elevations for extended periods of time. The main characteristic of this disease is a hemoglobin concentration greater than 21 g/dL for males or 19 g/dL for females. A diagnosis of CMS excludes chronic pulmonary disease or other conditions causing erythrocytosis and must include three of the following additional symptoms: breathlessness, palpitations, sleep disturbance, cyanosis, dilatation of veins, paresthesia, and headache (León-Velarde et al., 2005). Whereas the clinical characterization of CMS has been extensively detailed, the fundamental pathophysiologic process responsible for its development remains unclear.

Progression to a high altitude, especially in a short period of time, results in sleep-related breathing disorders and sleep architecture alterations (Goldenberg et al., 1992; Joern et al., 1970; Mizuno et al., 2005). These alterations are accompanied by frequent awakenings that are associated with pronounced oxygen desaturation, periodic breathing (PB), increased light non-rapid eye movement (NREM; sleep stages 1 and 2) sleep, and reduced deep NREM sleep (stages 3 and 4) (Panjwani et al., 2007). Nocturnal hypoxia and sleep disorders are also present in acute mountain sickness (Burgess et al., 2004; Erba et al., 2004; Nussbaumer-Ochsner et al., 2012a).

Although the sleep patterns of high-altitude natives and immigrants have previously been examined, the results are conflicting. Arai et al. (2002) reported that increased age in high-altitude Sherpa residents is associated with sleep desaturation. Coote et al. (1993) showed that the amount of slow wave rapid eye movement (REM) sleep of Peruvians living at 4300 m was similar to lowlanders, but they experienced episodes of PB and respiratory apneas that resulted in marked arterial desaturation. Sun et al. (1996) showed that disordered-breathing during sleep occurs with an equal, low frequency in young Tibetan and Han men. Plywaczewski et al. (2003) used a hypobaric chamber to simulate altitudes of up to 5000 m and showed that Tibetans had more episodes of PB, higher arterial oxygen saturation (SaO_2), and better sleep structure than Hans.

Only a few studies have examined the relationship between CMS and sleep architecture, with conflicting results. Spicuzza et al. (2004) found that Andean natives with excessive erythrocytosis (EE) had lower nighttime SaO_2 than controls and spent more time

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with SaO_2 < 80%, but no differences in the number and duration of apneas and hypopnoeas. Julian et al. (2013) compared the sleep of young males with EE and healthy controls in La Paz, Bolivia. They found that compared to controls, EE cases had a greater apnea–hypopnea index (AHI), a higher frequency of apneas (central and obstructive) and hypopnea during REM sleep, and lower nocturnal SaO_2.

Compared to Tibetan natives, Han Chinese show poor acclimatization to high altitude (Wu, 2004) and CMS is more common in immigrant Hans than indigenous Tibetans (Wu, 2005). However, the factors that predispose some immigrants to develop CMS are not well understood. In particular, it is unclear whether healthy immigrants residing at a high altitude for long periods of time suffer from sleep disturbances, whether there are differences in sleep disorders between immigrants that are healthy or have CMS, and to what extent these sleep disturbances correlate with CMS. In this study we tested the sleep structure, sleep-related breathing disorders, and nocturnal SaO_2 in immigrants with CMS and healthy controls residing at high elevations for long period of time.

2. Materials and methods

2.1. Subjects

The ethics committee of Qinghai University Medical College approved this study and informed consent was obtained from all subjects. This study was performed in the Yushu state of Qinghai province, China, at an altitude of 3780 m, from May 13 to July 13, 2012. Enrolled study subjects were ethnic Hans who had previously immigrated to a high altitude from the lower elevation plateau. All patients in this study had been living at a high altitude >5 year and had not ventured into the lower elevation plateau during the previous year. Immigrants were divided into CMS ($n = 14$) or control ($n = 11$) groups. The CMS group consisted of immigrants who were diagnosed with CMS (CMS score > 5) according to criteria from the consensus statement on chronic and subacute high altitude diseases (León-Velarde et al., 2005). Subjects in the control group had hemoglobin levels < 21 g/dL and a CMS score < 5. The control group was further subdivided, depending on whether the control patients suffered from sleep disturbances. Control subjects with an AHI ≥ 5 suffered from sleep disturbances and were placed in control group D. Control subjects with an AHI < 5 did not suffer from sleep disturbances and were placed in control group N. None of the study subjects had chronic obstructive pulmonary disease, chronic cor pulmonale, secondary erythrocytosis, or nervous system diseases.

2.2. CMS diagnosis and lung function

CMS was diagnosed according to the 2004 consensus statement on chronic and subacute high-altitude diseases (León-Velarde et al., 2005). Lung function in each patient was accessed by spirometry and flow-volume curves using a SpiroPro spirometer (Jaeger/Cardinal Health, Hoechberg, Germany). The pneumotachygraph was calibrated using a calibration syringe of known air volume.

2.3. Sleep study

Polysomnography (Somnomedics, Randersacker, Germany) was performed over the course of a full night of sleep and the following parameters were recorded from each patient: two electroencephalograms (two channels); two electrooculograms (left and right); chin electromyogram; nasal and mouth pressure air flow, thermal air flow; rib cage and abdominal movements; pulse oximetry; three lead electrocardiograms; oxyhemoglobin saturation using a finger probe; and body position measurements. Sleep studies were analyzed in 30 s epochs by two experienced polysomnograph technologists, following the American Academy of Sleep Medicine manual for the scoring of sleep and associated events and as the diagnosis standard (Iber et al., 2007).

The sleep parameters measured and analyzed were: total sleep time (TST); sleep efficiency (percentage of recording time spent asleep); percentage of TST that subjects spent in each sleep stage; arousal indices (arousals due to PB or upper airway obstruction, as well as spontaneous and total arousals); latency to sleep; and latency to REM sleep. An apnea was scored when airflow ceased for ≥10 s. A hypopnea was scored when the airflow was <30% of baseline for 10 s or longer and desaturation ≥4% from pre-event baseline. A central apnea was scored when there was a cessation of airflow and absent inspiratory effort. Obstructive apneas were scored when there was a cessation of airflow that was associated with continued or increased inspiratory effort. A mixed apnea was scored when there was a cessation of airflow that was associated with absent inspiratory effort in the initial portion of the event, followed by resumption of inspiratory effort in the second portion of the event. PB was scored when five or more central apneas or hypopneas per hour of sleep occurred and was accompanied by ≥10 consecutive min of a cyclic crescendo and decrescendo change in breathing amplitude.

2.4. Statistical analysis

Statistics were carried out using SPSS 19.0 software (IBM Corp., Armonk, NY, USA). Differences among groups were analyzed using one-way analyses of variance or the Kruskal–Wallis H-test. A Pearson's correlation coefficient was used to assess correlations between parameters. Data are presented as mean ± standard error or as median (lower quartile, upper quartile); a $P < 0.05$ was considered as statistically significant.

3. Results

The patients' histories and physical characteristics of enrolled subjects were recorded. No significant differences were observed between the CMS and either control group with respect to age, body mass index, length of time living in a plateau, or lung function (Table 1).

3.1. Sleep variables

The mean TST of both groups was >400 min and the sleep efficiency was >80%. No significant differences were observed between the CMS patients and either control group with regard to TST, sleep efficiency, NREM sleep (stages 1, 2, 3, or 4), length of REM sleep, or the arousal index (Table 2). The percentage of sleep time spent in deep NREM sleep (stage 3 and 4) was significantly lower in the CMS and control D groups compared to the control N group (Ps < 0.05), whereas the latencies to NREM stage 1 and 2 and deep NREM sleep did not differ. REM latency was significantly lower in the control groups compared to the CMS group ($P = 0.018$). Finally, REM latency in the control N group was lower than in the control D group.

3.2. Respiratory variables

The AHI and hypopnea index in the CMS and control D groups were significantly higher than in the control N group (Ps < 0.01); there was no significant difference between the CMS and control D groups. Hypopnea was the most prevalent type of sleep disorder in both the CMS and control D groups. No significant differences in the central, obstructive, or mixed apnea indices were observed among the groups. In most cases, subjects presented with central apnea and hypopnea, whereas a fewer number of cases presented